REMARKS

I. Petition for Extension of Time

In response to the final Office Action, mailed January 11, 2005, Applicants petitioned for a one-month extension of time and submitted an amendment on April 29, 2005. The Office issued an Advisory Action, mailed May 17, 2005. The proposed amendment was not entered because it allegedly raised new issues requiring further consideration and/or search.

Applicants now petition for a second one-month extension of time extending the time for response to the final Office Action to June 11, 2005, or the first following business day. Authorization is hereby given to charge the extension of time fee of **$330.00** ($450-$120 = $330) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

II. Claim Amendments

The amendment filed May 17, 2005 in response to the final Office Action was not entered for the reasons given in the Advisory Action. **Applicants do not wish to have the previously filed and unentered amendment entered. Applicants request non-entry of the amendment filed May 17, 2005.**

Applicants request entry and consideration of this amendment which is being filed concurrently with and as part of their RCE.

Claim 1 has been amended to clarify that the core excipient, i.e., one or more alkaline additives, is an alkalizing agent present in the core in a sufficiently high amount to neutralize the absorbed acidic fluid and protect the active ingredient against degradation (See page 4, lines 13-15). Specifically, claim 1 has been amended to recite that the alkalizing agent is an alkaline agent present in an amount of approximately 10-35% by weight of the core material excluding the weight of an optional starter seed (See page 6, line 27). Support for the amendment is provided by the specification at page 6, line 27. Claim 1 has been further amended to recite that the semipermeable membrane "consists of", as opposed to consists essentially of, the recited ingredients.

Claims 6, 12, 14, and 15 have been amended to recite -- starter seed --, as opposed to "sugar sphere", in view of the antecedent basis provided by amended claim 1. Support is found at page 5, line 21 of the specification, which provides that the core material may be produced with starter seeds. New claim 29 is supported by the specification at page 5, lines 19-21.

Applicants submit that no new matter has been introduced by any of the claim amendments.

III. Claim Rejections – 35 U.S.C. §103(a)

A. US 6,245,351 to Nara et al. ("Nara")

Claims 1, 3, 6-18, 20 and 25-28 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over US 6,245,351 to Nara et al. ("Nara"). The claims haven been amended to clarify the patentably distinguishing features of the claimed invention over Nara.

1. Nara does not suggest the need for a high amount of an alkalizing agent in the core comprising an acid-labile active ingredient.

The active ingredient of the claimed dosage form is an acid-labile substance, e.g., omeprazole. It is established that an oral, solid dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. The enteric coated formulation offers the best possibility of transporting the acid-labile active ingredient down to the small intestine where it is released and absorbed. The prior art is replete with disclosures of enteric coated formulations comprising omeprazole or other proton pump inhibitor compounds.

Surprisingly, and contrary to the teaching of the prior art, Applicants have developed a solid, oral formulation of omeprazole that is not enteric coated. The claimed oral dosage form comprises a core material that is coated with a semipermeable membrane that disrupts to provide a delayed release of the acid-labile active ingredient in the small intestine. Claim 1 has been amended to clarify that the core material also comprises a sufficiently large amount of an alkalizing agent (specification at page 4, lines 10-15).

In the absence of an enteric coating, the diffusion of acidic gastric fluids through the semipermeable membrane will almost immediately cause degradation of the omeprazole

compound. Advantageously, the incorporation of an alkalizing agent in the core material together with the active ingredient acts to neutralize acidic gastric fluids adsorbed through the semipermeable membrane while the dosage form, passes through the stomach en route to the small intestine. To effectively counter the absorbed acidic fluid and protect the acid-labile drug, the alkalizing agent must be present in a sufficiently high amount to protect the acid-labile, active ingredient against degradation, e.g., preferably 10 to 35% by weight calculated on the weight of the core material excluding the weight of an optional starter seed (specification at page 6, line 27).

Nara does not suggest the inclusion of a high amount of an alkalizing agent in the core. This is no surprise since Nara discloses a broad range of other possible active ingredients (col. 3, lines 35-63), including omeprazole and lansoprazole, without giving any attention to or recognition of the unique problems relating to formulation of dosage forms having an acid-labile substance as the active ingredient. These formulation problems become even more complicated for acid-labile drugs when the dosage form is not enteric coated. Such formulation concerns may be irrelevant with opioid compounds which are expressly preferred by Nara (col. 3,lines 65). It is evident, therefore, that Nara fails to recognize the unique problems associated with the development of solid, oral formulations of acid-labile drugs and the need to protect the acid-labile drugs from the acidic environment of the stomach, especially when the dosage form is not enteric coated.

Nara discloses the possibility of including a lubricant , such as talc, in the core (col. 5, lines 51-53). However, Nara does not expressly disclose the amount of lubricant to be present in the core. Applicants submits that the person of ordinary skill in the art of pharmaceutical formulations would know that the amount of lubricant in the core of a dosage form is less than the high amount of alkalizing agent, i.e., 10 to 35% as required by the claimed invention. As part of this communication, Applicants are submitting a copy of page 328 from "The Theory and Practice of Industrial Pharmacy", Third Edition (1986) which discloses that talc, when used as a glidant or flow promoter, is typically present in a formulation at a 5% concentration. As such, the optional inclusion of a lubricant in the core as disclosed by Nara is different from the function of the alkalizing agent which is present in a sufficiently high amount in the core of the claimed invention.

The inclusion of a sufficiently high amount of an alkalizing agent in the core of the claimed invention provides a superior advantage over the composition disclosed by Nara when the core material comprises an acid-labile substance and the dosage form is not enteric coated.

2. **The semipermeable membrane of the claimed invention does not contain a hydrophilic substance and swellable agent as disclosed by Nara.**

Claim 1 has been further amended to recite that the semipermeable membrane "consists of", as opposed to consists essentially of, the recited ingredients. Thus, the semipermeable membrane of the claimed invention is defined by a water-insoluble polymer and a modifying agent. In contrast, the coating composition disclosed by Nara contains a hydrophilic substance and a swellable agent, both of which are excluded from the semipermeable membrane of the claimed invention.

Therefore, it is the swelling agent in the core of the claimed invention that expands upon exposure to the fluid or moisture absorbed through the semipermeable membrane (specification at page 4, lines 15-19). After a pre-determined time interval, the expansion of the swelling agent in the core of the claimed invention leads to a disruption of the semipermeable membrane by the built-up pressure. As such, the semipermeable membrane of the claimed invention disrupts notwithstanding the absence of a swelling agent in the membrane as required by Nara.

3. **The composition, structure and release mechanism of the claimed dosage form are different and not suggested by Nara.**

Advantageously, the core material of the claimed dosage form includes an alkalizing agent in a sufficiently high amount to protect the acid-labile active ingredient from degradation. Nara does not recognize or acknowledge the unique problems relating to formulation of a dosage form, which is not enteric coated, having an acid-labile substance as the active ingredient. Finally, release of the active ingredient of the claimed invention is achieved without the presence of a swelling agent in the semipermeable membrane as required by Nara. Rather, the swelling agent present in the core of the claimed dosage form expands which leads to a disruption of the semipermeable membrane by the built-up pressure.

For all of the foregoing reasons, therefore, Applicants respectfully submit that the structure and advantages of the claimed invention formulation are not suggested by Nara. Withdrawal of the §103 rejection based on Nara is requested.

B. Nara in view of WO 98/54171

Claims 4, 5 and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view WO 98/54171 in the name of Cotton et al. ("Cotton").

As stated by the Examiner on page 4 of the Office Action, Cotton is cited for the disclosure of the magnesium salt of S-omeprazole as an active ingredient.
Applicants submit that Cotton does not over come the deficiencies of Nara to suggest the claimed invention for the reasons given in the preceding Section. Withdrawal of the §103 rejection based on Nara in view of Cotton is requested.

CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. It is respectfully submitted that claims 1, 3-10, 12-18, 20 and 23-29 are in condition for allowance, which action is earnestly solicited.

Any fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: 13 June 2005

Respectfully submitted,

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Enclosures:

1. Form PTO/SB/30 (1 page)
2. The Theory and Practice of Industrial Pharmacy, Third Edition (1986), p .328 (4 pages)

The Theory and Practice of Industrial Pharmacy

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The Theory and Practice of Industrial Pharmacy

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solution to provide an anhydrous adhesive. Ethylcellulose may be used only as an alcoholic solution, and it may be expected to retard disintegration and dissolution time of drugs in the resulting tablets when wet granulation is employed. Polyvinylpyrrolidone is a synthetic polymer that may be used as an adhesive in either an aqueous solution or alcohol. It also has some capabilities as a dry binder.

Disintegrants

A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when it contacts water in the gastrointestinal tract. Disintegrants may function by drawing water into the tablet, swelling, and causing the tablet to burst apart. Such tablet fragmentation may be critical to the subsequent dissolution of the drug and to the attainment of satisfactory drug bioavailability. Starch USP and various starch derivatives are the most common disintegrating agents. They also have the lowest cost. Starch is typically used in a concentration range of 5 to 20% of tablet weight. Such modified starches as Primogel and Explotab, which are low substituted carboxylmethyl starches, are used in lower concentrations (1 to 8%, with 4% usually reported as optimum). Various pregelatinized starches are also employed as disintegrants, usually in a 5% concentration.

Clays such as Veegum HV and bentonite have been used as disintegrants at about a 10% level. Such use of these materials is limited unless the tablets are colored, since the clays produce an off-white appearance. The clays are typically less effective as disintegrants than some of the newer modified polymers and starches, which can increase in volume in the presence of water by 200 to 500%. The disintegrating characteristics of microcrystalline cellulose have been reported previously in this chapter; however, in the cellulose class, a new material known as Ac-Di-Sol is now available and is effective in low concentration levels. It is an internally cross-linked form of sodium carboxymethylcellulose. Another cross-linked polymer that is available as a disintegrant is cross-linked polyvinylpyrrolidone.

Lubricants, Antiadherents, and Glidants

These three classes of materials are typically described together because they have overlapping functions. A material that is primarily described as an antiadherent is typically also a lubricant, with some glidant properties as well. The differentiation between these terms is as follows: Lubricants are intended to reduce the friction during tablet ejection between the walls of the tablet and the walls of the die cavity in which the tablet was formed. Antiadherents have the purpose of reducing sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall. Glidants are intended to promote flow of the tablet granulation or powder materials by reducing friction between the particles.

In addition to the lubricants listed in Table 11-4, hydrocarbon oils such as mineral oil have been employed by application to granulation as a fine spray, either directly or in a solvent solution. The problem with using this type of lubricant is the production of oil spots. The most widely used lubricants have been stearic acid and various stearic acid salts and derivatives. Calcium and magnesium stearate are the most common salts employed. Stearic acid is a less effective lubricant than these salts and also has a lower melting point. Talc is probably the second most commonly used tablet lubricant, historically. Most talc samples are found to contain trace quantities of iron, and talc should be considered carefully in any formulation containing a drug whose breakdown is catalyzed by the presence of iron. The higher-molecular-weight polyethylene glycols and certain polymeric surfactants have been used as water-soluble lubricants. These materials are much less effective as lubricants, however, than the materials previously cited. Since lubrication is basically a coating process, the finer the particle size of the lubricant, the more effective the lubricant action is likely to be.

As previously noted, most of the materials listed as lubricants, with the possible exception of those that are water-soluble, also function as antiadherents. Talc, magnesium stearate, and starch as well as starch derivatives possess antiadherent properties. In addition, various colloidal silicas have been used as antiadherents.

Materials used as glidants, or flow promoters, are typically talc at a 5% concentration, corn starch at a 5 to 10% concentration, or colloidal silicas such as Cab-O-Sil, Syloid, or Aerosil in 0.25 to 3% concentrations.

Colors, Flavors and Sweeteners

The use of colors and dyes in tablet making has served three purposes over the years: disguising of off-color drugs, product identification, and production of a more elegant product. With the continual decertification of many synthetic